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(54) Title: A STABLE BENZIMIDIAZOLE FORMULATION

(57) Abstract: A stable oral pharmaceutical composition containing a Benzimidazole compound or its pharmaceutically acceptable salt wherein the active ingredient is coated with an enteric coating polymer and has no separating or protective layer in between. These pellets can be filled in to the capsules or compressed into Tablets. Further disclosed is a method for the manufacture of such a formulation, and the use of such a formulation in medicine.

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A STABLE BENZIMIDIAZOLE FORMULATION

Field of the invention

The present invention relates to an oral pharmaceutical formulation or composition containing a benzimidiazole compound. More particularly, the present invention relates to an oral pharmaceutical formulation or composition containing a benzimidiazole compound in the form of a capsule, tablet or pellets.

Background of Invention & Prior Art:

Omeprazole and its pharmaceutically acceptable salts, is known to be useful for inhibiting gastric acid secretion by controlling gastric acid secretion at the final step of the acid secretary pathway. Omeprazole shows a powerful inhibitory action against secretion of gastric juice (Lancet, Nov. 27, 1982, p. 1223-1224).

Omeprazole is however susceptible to degradation and transformation in acidic and neutral media. The half-life of omeprazole in water solutions at pH-values less than four is shorter than ten minutes. At pH 7, the degradation reaction proceeds rapidly and the half-life of omeprazole is about 14 hours, while at higher pH-values the stability in solution is much better (Pilbrant and Cederberg, Scand. J. Gastroenterology 1985; 20 (supp. 108) p. 113-120). The stability profile is similar in solid phase. The degradation of omeprazole is catalyzed by acidic reacting compounds and is stabilized in mixtures with alkaline reacting compounds. The stability of omeprazole is also further affected by moisture, heat, organic solvents and to some degree by light.

The current practice known in the Art is to put a separating / barrier layer in between the drug core and the enteric coat as to prevent the interaction among the acidic polymer and the drug. Ordinary enteric coatings, however, are made of acidic compounds. If covered with such a conventional enteric coating, omeprazole rapidly decomposes by direct or indirect contact with it, with the result that the preparations become badly discolored and loss in omeprazole content decreased with the passage of time.

A fully bioavailable dosage form of omeprazole must release the active drug rapidly in the proximal part of the gastrointestinal canal. An oral dosage form of omeprazole must be protected from contact with the acidic gastric juice in order to

reach the small intestine without degradation where pH is near 6.8 and where rapid absorption can occur.

Thus, there has been a need to develop an enteric coating layered multiple unit preparations such as divisible and/or dispersible tablets of omeprazole with good chemical stability as well as improved mechanical stability making it possible to produce well functioning and patient-friendly packages that will result in improved patient acceptance.

In the present invention, the separating layer is avoided and the cores of the drug are provided with a direct enteric coat without resort to the separating layer. The formulation obtained as per the present invention is easier to package and the delivery of the formulation to the patient will be intact at the time of opening the package. According to the present invention only an enteric coating layered multiple units tablet can be made divisible and dispersible. A further advantage of a multiple unit dosage form is that it disperses into a multitude of small units in the stomach upon administration.

A further object of the invention is to provide a multiple unit tablet dosage form, which are divisible and easy to handle. Such a multiple unit tablet dosage form may be dispersed in an aqueous liquid and can be given to patients with swallowing disorders and in pediatrics. Such a suspension of dispersed units or pellets of appropriate size can be used for oral administration.

US Patent 4853230 describes an enteric coated pellet comprising of Omeprazole with alkaline compound as a core material having sub coat consisting of one or more of magnesium oxide, magnesium hydroxide or their composite and HPMC, HPC or PVP as a polymer.

US Patent 5690960 states that magnesium salt of Omeprazole may be formulated as an enteric-coated tablet after compressing the granules. The enteric coated pellets of S- Omeprazole of disclosed patent may be filled in HGC. In both the cases, before applying the enteric coating to core material, it is required to sub coat the core material.

US Patent 3132771 discloses a formulation of S- omeprazole magnesium in a form of enteric coated multiple unit with one or more prokinetic agents in the form of a powder or granules compressed into a tablet or in the form of capsule.

US Patent 6174548 describes an enteric coated formulation consisting of Omeprazole, a surface active agent, a filler, a binder and a alkaline agent (lysine or arginine). The enteric coating was applied without sub coating the core material.

US Patent 6391342 describes an oral formulation comprising granules having Omeprazole, a disintegrant and a surfactant in a meltable matrix. The granules/pellets were sub coated and then enteric coating was applied.

US Patent 6,428,810 describes an enteric-coated oral dosage form comprising of the magnesium salt of Omeprazole in the form of multiple unit dosage form. The sub coating on the core material was applied using hydroxypropyl cellulose as a polymer.

US Patent 4786505 describes an enteric-coated omeprazole preparation containing a separating subcoat between the core material and the enteric coating. This preparation contains an alkaline core comprising omeprazole, a subcoating and an enteric coating. The present invention as disclosed herein does not use an alkaline agent.

OBJECTS OF THE INVENTION

It is an object of the present invention to provide an enteric coated benzimidiazole pharmaceutical formulation without a barrier coat between the drug core and the enteric coat.

Further object of the invention is to create a dosage form that disperses into a multitude of small units in the stomach upon administration.

Another object of the invention is to provide a multiple unit tablet dosage form, which are divisible and easy to handle.

SUMMARY OF THE INVENTION:

The invention relates to a method of manufacturing a benzimidiazole formulation wherein the active medicament is sprayed onto a core material such as sugar or non-pareil seeds. These beads are then directly coated with an outer layer comprising of an enteric coating without a separating layer in between. The pellets so formed are filled in capsules. Even without the separating layer, the formulation so formed according to the present invention is stable.

DETAILED DESCRIPTION OF THE INVENTION:

Non-pareil seeds or sugar crystals can be used for making the core material of the formulation. The core material for the individually enteric coating layered pellets

can be constituted according to known principles. The seeds, which are layered with the active substance, can be water insoluble seeds comprising different oxides, celluloses, organic polymers and other materials, alone or in mixtures thereof or water soluble seeds comprising different inorganic salts, sugars and other materials, alone or in mixtures thereof. The size of the seeds may vary between 0.1 and 4 mm and preferably between 0.1 and 2 mm.

The core material is placed in a conventional coating pan or fluidized bed and then the active drug (a benzimidiazole such as omeprazole, rabeprazole, lansoprazole, pantoprazole or one of their single enantiomers or their alkaline salts or their single enantiomers) along with additional constituents such as binders, anti-adherents, lubricant, surfactants and water are sprayed onto such core material.

The seeds or sugar crystals layered with active substance are produced either by powder or solution/suspension layering or by spray coating or layering equipment. Before the seeds are layered, the active substance may be mixed with further components. Such components may be binders, lubricants, anti adherents or other pharmaceutically acceptable ingredients, alone or in mixtures, as processing aids.

The binders used include, for example, celluloses, hydroxypropyl methylcellulose, polyethylene glycol, hydroxypropyl cellulose, carboxymethyl-cellulose sodium, polyvinyl pyrrolidone and other pharmaceutically acceptable substances with cohesive properties, including natural gums.

Suitable solubilizers having HLB value greater than 3 and preferably greater than 5, such as medium chain triglycerides not limited to Caprylocaryroyl Macrogol Glycerides (Labrasol), Lauroyl Macrogol glycerides (Gelucire), Oleoyl Macrogol Glycerides (Labrafil), Polyoxyethylene castor oil derivaties such as Polyoxyl 35 Castor oil (Cremophore EL), can be used. Suitable surfactants such as sodium lauryl sulfate or polysorbates (eg. Tween) can be used. Anti-adherent substances such as talc, colloidal silicon dioxide, calcium silicate, silica gel or combinations thereof are used.

The above items are mixed with water to obtain dispersion. The active drug is mixed with the above dispersion. The dispersion or solution of suitable binder is added to the drug dispersion. This dispersion is utilised to coat the non pareil seeds/ sugar crystals.

Enteric coating layer

Enteric coating layers are applied onto the pellets or particles using a suitable coating technique such as pan coating or fluidized bed coating. The enteric coating layer material may be dispersed or dissolved in either water or in suitable organic solvents or a combination thereof or by using latex suspensions of said polymers. The percentage of w/w enteric coating layer may be from 10 to 90%, more preferably, from 05 to 55% w/w of the core material.

The pellets so formed are then coated with an enteric coating material such as Poly (methacrylic acid, methyl methacrylate), commonly known as Eudragit L and S type, aqeous dispersion of Poly (methacrylic acid, ethyl acrylate) known as Eudrgit L 30D- 55, Poly (ethyl acrylate, methyl methacrylate) known as Eudrgit NE 30 D, Poly (ethyl acrylate, methyl methacrylate, trimethylamonioethyl methacrylate chloride) known as Eudragit RS. Cellulosic enteric coating materials such as cellulose acetate Phthalate, hydroxypropyl methylcellulose phthalate, polyvinyl acetate phthalate, carboxymethyl ethylcellulose. These pellets are then filled in capsules. The enteric coating can also be applied using water-based polymer dispersions, e.g. Aquateric^{RTM} (FMC Corporation), or suitable combination of any of these. The pH of the coating solution is adjusted by adding ammonia solution if required for neutralization.

The enteric coating layer can optionally contain a pharmaceutically acceptable plasticizer such as cetanol, triacetin, triethyl citrate, glyceryl monostearate, polyethylene glycol, citric acid esters, phthalic acid esters, dibutyl succinate or similar plasticizers. The amount of plasticizer is optimized for each enteric coating layer formula, in relation to selected enteric coating layer polymer(s), selected plasticizer(s) and the applied amount of said polymer(s) and is usually above 10% by weight of the enteric coating layer polymer(s), preferably 15-50%, and more preferably 20-50%.

Additives such as dispersants, colorants, pigments, polymers e.g. poly(ethylacrylate, methylmethacrylate), may also be included into the enteric coating layer(s).

The pellets that have been so coated by the enteric coat are ready for dosing by various methods such as further packing in sachets or pellets formulated into tablets using various processes known in the art, filling into or hard gelatin capsules.

The present invention will now be described with refernce to the following non-limiting Examples:

Example 1

Drug Layering on non-pareil seeds and Enteric coating of the same

Table 1

Ingredient	**Quantity (g)**
Sugar beads	1000
Composition of coating solution **Drug layer (1A)**	
Omeprazole	**200**
Hydroxypropyl methyl cellulose (6cps)	**240**
Talc	**200**
Purified Water	**q.s.**
Enteric Coating (1B)	
Drug layered pellets of step 1A	**500**
EudragitL30D-55	**690**
Triethyl Citrate	**19.15**
Talc	**24.24**
Ammonia solution (30%)	**q.s**
Purified Water	**q.s.**

Preparation of coating solution

Hydroxypropyl methylcellulose was dispersed in warm, purified water. Micronised talc was dispersed in water with constant stirring in a colloidal mill. Omeprazole was added to the talc dispersion. Aqueous dispersion of HPMC was added to the omeprazole dispersion. Sufficient amount of purified water was added to adjust the required volume/ strength of coating solution. The sugar beads were coated using above coating solution in a fluid bed coater.

Enteric coating

Eudragit L 30D- 55 was dispersed in purified water. Talc was added to purified water. The pH of Eudragit-L dispersion was adjusted to 4.5 to 5.5 using dilute ammonia solution. Eudragit dispersion was added slowly into the talc dispersion with constant stirring. The pH of the final dispersion may be adjusted between 5.3 and 5.4, as necessary using ammonia solution. Drug layered sugar beads are coated using Eudragit dispersion in a fluid bed coater. The coated pellets can be filled in hard gelatin capsules.

When tested 99.3. to 100 % drug was released with in 30 minutes. The unit dose pellets contains less than 0.7 % related substances. The gastro resistance is found to be 1.81%.

Example 2

Drug Layering on graded sugar crystals and Enteric coating of the same

Composition of the coating solution and enteric coating solution is same as described under the example 1. Instead of sugar beads, graded sugar crystals were used. The coated pellets were encapsulated in hard gelatin capsule shells.

Example 3 (addition of colour to Sample of Eg. 1)

Drug layered sugar crystals of example 2 were enteric coated using the enteric coating formula of Table 1 (example 1) and Ponceu 4R lake (see Table 2). **Preparation is same as described under example 1**; only Ponceu 4R lake is added along with Talc. The enteric coating conditions and procedure was same as described under example 1.

Table2

Ingredients	**Quantity (grams)**
Omeprazole loaded sugar crystals	700.00
Eudragit L30D-55	953.00
Triethyl Citrate	26.45
Talc	33.48
Ponceu 4R lake	4.13
Ammonia solution (25 %) (To adjust the pH to 5.4 to 5.5)	q.s.
Purified Water	q.s.

Example 4

Drug layered sugar crystals of example 2 were enteric coated using the enteric coating formula of Table 1 (example 1), Preparation is same as described under example 1, only the Ponceu 4R lake, Iron oxide red and Polyethylene glycol 6000 is added along with Talc. The enteric coating procedure is same as described under example 1.

Table 3

Ingredients	Quantity (grams)
Omeprazole loaded sugar crystals	700.00
Eudragit L30D-55	953.00
Triethyl Citrate	26.45
Talc	33.48
Iron oxide red	4.13
Polyethylene glycol 6000	2.65
Ammonia solution (25 %) (To adjust the pH to 5.4 to 5.5)	q.s.
Purified Water	q.s.

EXAMPLE - 5

Table 4

Drug layered crystals of example 2 were enteric coated

The procedure of Example 2 was carried out except that Surfactant (Tween 80) and Glyceryl monostearate was included in the formulation.

Ingredients	Quantity (grams)
Omeprazole loaded sugar non pareil seeds	550.00
Eudragit L30D-55	250
Triethyl Citrate	97.5
Glyceryl monostearate	32.5

Tween-80	13.00
Iron Oxide Red	3.2
Water	q.s.

EXAMPLE – 6

Drug Layering on non-pareill seeds and Enteric coating of the same

Table 5	
Ingredient	**Quantity (g)**
Sugar beads	1000
Composition of coating solution **Drug layering (5A)**	
Omeprazole	**200**
Hydroxypropyl methyl cellulose (6cps)	**240**
Talc	**200**
Cremophore EL	**20**
Purified Water	**q.s.**
Enteric Coating (5B)	
Drug layered pellets of step 5A	**500**
EudragitL30D-55	**690**
Triethyl Citrate	**19.15**
Talc	**24.24**
Ammonia solution (30%) **(To adjust the pH to 4.5 to 5.5)**	**q.s**
Purified Water	**q.s.**

Preparation of coating solution

1. Hydroxypropyl methylcellulose is dispersed in warm, purified water.
2. Cremophore EL is dispersed in water separately.
3. Micronised talc is added to the Cremophore dispersion with constant stirring in a colloidal mill.
4. Omeprazole is dispersed in this dispersion.

5. Aqueous dispersion of HPMC is added to the dispersion from step 4.
6. Sufficient amount of purified water is added to adjust the required volume/ strength of coating solution. The sugar beads are coated using above coating solution in a fluid bed coater.

Enteric coating

Enteric coating was carried out by the procedure described in Example 1.

EXAMPLE – 7

The entire procedure in Example 6 was followed, except that Labrasol was substituted by Cremophore.

Example- 8

Drug Layering (Rabeprazole) on non-pareil seeds and Enteric coating of the same

Table 6

Ingredient	**Quantity (g)**
Non- Preil Seeds	1000
Composition of coating solution **Drug layer (6A)**	
Rabeprazole	**240**
Hydroxypropyl methyl cellulose	**200**
Talc	**400**
Glucire	**3.0**
Purified Water	**q.s.**
Enteric Coating (6B)	
Drug layered pellets of step 1A	**500**
EudragitL30D-55	**290**
Triethyl Citrate	**9.0**
Talc	**84.0**

Ammonia solution (30%)	**q.s**
Purified Water	**q.s.**

The entire procedure in Example 6 was followed. The only change was the substitution of Cremophore with Gelucire and rabeprazole with omeprazole.

Example 9

Formulation of Tablet

Enteric coated pellets of Example 8 were mixed with microcrystalline cellulose, Crospovidone and sodium steryl fumarate. The blend was compressed into tablets. The tablets are film coated with hydroxyproyl methylcellulose, polyethylene glycol upto 2 percentage gain by weight

Table 7

	Quantity (grams)
Enteric coated Pellets of Example 8	175
Microcrystalline cellulose	200
Crospovidone	25
Sodium steryl fumarate	5

We claim:

1. An oral pharmaceutical composition comprising:
   a) a core comprising an effective amount of a benzimidiazole compound or its pharmaceutically acceptable salt, a core substrate and at least one binder;
   b) an enteric coated outer layer disposed on the said core.

2. A pharmaceutical composition as claimed in claim 1 comprising:
   a) a core comprising an effective amount of a benzimidiazole compound or its pharmaceutically acceptable salt, a solubilizer having Hydrophilic Lipophilic Balance value of at least 3, at least 0.1% w/w of a binder and a core substrate.
   b) an enteric coated outer layer disposed on the said core without placing a barrier coat between the said core & the enteric coated outer layer such that the enteric coating material is between 5-55% (preferably 15-45%) w/w of the core.

3. A pharmaceutical composition as claimed in claim 1, optionally containing one or more pharmaceutically acceptable additives selected from group consisting of: anti-adhering agents (glidant); diluents; plasticizers.

4. A pharmaceutical composition as claimed in any preceding claim wherein said formulation is in form of capsules that are filled by pellets as obtained in claim 1.

5. A pharmaceutical composition as claimed in claim 1 wherein said pellets are compressed with pone or more pharmaceutically acceptable adjuvants such as anti-adhering agents (glidant); diluents to form tablets.

6. A pharmaceutical composition as claimed in claim 1 wherein the beziimidiazole compound
   is selected from, but not limited to, a group consisting of Omeprazole, Rabeprazole, Lansoprazole, Pantoprazole or their pharmaceutically acceptable alkaline salts.

7. A pharmaceutical composition as claimed in claim 1, wherein said core is made up of material selected from a group comprising sugar crystals, non pareil seeds, microcrystalline cellulose, starch or any combination thereof.

8. A pharmaceutical composition as claimed in claim 1, wherein the solubilizer has a Hydrophilic Lipophilic Balance value of at least 3 and preferably greater than 5, and is selected from, but not limited to, a group consisting of sodium lauryl sulfate, polysorbates, medium chain triglycerides such as Caprylocaryroyl Macrogol Glycerides, Lauroyl Macrogol glycerides, Oleoyl Macrogol Glycerides, Polyoxyethylene castor oil derivatives such as Polyoxyl 35 Castor oil.

9. A pharmaceutical composition as claimed in claim 1, wherein said binder is selected, but not limited to, from a group of a water soluble materials consisting of celluloses, hydroxypropyl methylcellulose, hydroxypropyl cellulose, carboxymethyl-cellulose sodium, polyvinyl pyrrolidone, Sugar, natural gums.

10. A pharmaceutical composition according to claim 1 wherein the enteric coated layer is selected from a group consisting of cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, Polyvinyl acetate phthalate, carboxymethylethylcellulose, co polymer of ethyl acrylate and methyl methacrylate, co-polymerized methacrylic acid or acid methyl esters, partially neutralized solutions or dispersions of such polymers.

11. A pharmaceutical composition as claimed in claim 3, wherein the anti-adhering agent is selected from a group consisting of talc, colloidal silicon dioxide, calcium silicate, silica gel, aluminium magnesium hydroxide and silicates thereof.

12. A pharmaceutical composition as claimed in claim 3, wherein the diluent is selected from a group consisting of Lactose, Microcrystalline cellulose, sugar, starch, cellulose.

13. A pharmaceutical composition as claimed in claim 3, wherein the plasticizer is selected from a group consisting of: cetanol, triacetin, triethyl citrate, glyceryl monostearate, polyethylene glycol, citric acid esters, phthalic acid esters, dibutyl succinate.

14. A process for the preparation of an oral pharmaceutical composition containing a benzimidazole, comprising:

i) mixing a solubilizer, an anti-adhering agent and benzimidazole compound into water to form a separate dispersion;

ii) addition to said dispersion, binder and water

iii) coating non-pareil seeds with the dispersion obtained from step (c) to obtain drug layered seds;

iv) coating said drug layered seeds with an enteric coating polymer and optionally a plasticizer to form pellets.

15. A process as claimed in claim 13 wherein said pellets are filled into capsules.

16. A process as claimed in claim 13 wherein said pellets are compressed into tablets along with pharmaceutically acceptable adjuvants.

17. A process as claimed in claim 13 wherein said anti-adhereing agent includes glidant; diluents and plasticizers.

18. A process as claimed in claim 13 wherein said wherein the benzimidiazole compound is selected from, but not limited to, a group consisting of Omeprazole, Rabeprazole, Lansoprazole, Pantoprazole or their pharmaceutically acceptable alkaline salts.

19. A process as claimed in claim 13 wherein said wherein the solubilizer has a Hydrophilic Lipophilic Balance value of at least 3 and preferably greater than 5, and is selected from, but not limited to, a group consisting of sodium lauryl sulfate, polysorbates, medium chain triglycerides such as Caprylocaryroyl Macrogol

Glycerides, Lauroyl Macrogol glycerides, Oleoyl Macrogol Glycerides, Polyoxyethylene castor oil derivatives such as Polyoxyl 35 Castor oil.

20. A process as claimed in claim 13 wherein said wherein said binder is selected, but not limited to, from a group of a water soluble materials consisting of celluloses, hydroxypropyl methylcellulose, hydroxypropyl cellulose, carboxymethyl-cellulose sodium, polyvinyl pyrrolidone, Sugar, natural gums.

21. A process as claimed in claim 13 wherein said wherein the enteric coated layer is selected from a group consisting of cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, Polyvinyl acetate phthalate, carboxymethylethylcellulose, co polymer of ethyl acrylate and methyl methacrylate, co-polymerized methacrylic acid or acid methyl esters, partially neutralized solutions or dispersions of such polymers.

22. A process as claimed in claim 13 wherein said, wherein the anti-adhering agent is selected from a group consisting of talc, colloidal silicon dioxide, calcium silicate, silica gel, aluminium magnesium hydroxide & silicates thereof.

23. A process as claimed in claim 13 wherein said wherein the diluent is selected from a group consisting of Lactose, Microcrystalline cellulose, sugar, starch, cellulose.

24. A process as claimed in claim 13 wherein said wherein the plasticizer is selected from a group consisting of: cetanol, triacetin, triethyl citrate, glyceryl monostearate, polyethylene glycol, citric acid esters, phthalic acid esters, dibutyl succinate.

25. A method for the treatment of gastrointestinal disease comprising administering to a host in need of such treatment a therapeutically effective amount of a preparation according to claim 1.